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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,410	01/18/2005	Axel Ullrich	2923-679	7025

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
01/26/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,410	ULLRICH ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-34* is/are pending in the application.

4a) Of the above claim(s) *1-9,11,13 and 20-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,12,14, 17-19 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 14, 2008 has been entered.

2. Claims 1-14 and 17-34 are pending.

3. Claims 1-9, 11, 13, and 20-34 have been previously withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions protein as previously set forth in the Office Action of October 19, 2007.

4. Claims 10, 12, 14, 17-19 and 35 are currently under consideration drawn to the AXL protein and the species of an antibody directed against the AXL protein as previously set forth in the Office Action of October 19, 2007.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 10, 12, 14, 17-19 and 35 remain rejected essentially for the reasons set under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement essentially for the reasons set forth in the Office Action of May 14, 2007, sections 4-pages 2-5.

Examiner argued in the Office Action of May 14, 2007:

Applicants argue that the specification provides in vivo and reliable in vitro data to support the pending claims. The specification provides in vivo data from tumor cells subcutaneously implanted into nude mice (a reliable model) with subsequent intravital microscopy and histomorphological analyses. See Figure 9 and p. 13, line 20- p.14, line 16; p. 33, line 15 - p. 34, line 25, p. 35, line 24 - p. 36, line 13; Figure 11 and p. 15, lines 9-16 of the present specification. The results here showed impaired tumorigenicity, reduced tumor growth, lack of tumor invasion, and increased sensitivity towards serum withdrawal (apoptosis) after implantation of cells with a truncated, dominant-negative mutant form of human UFO/AXL lacking the intracellular RTK-bearing domain. See p. 32, line 22- p. 33, line 5; p. 33, line 15- p. 34, line 13; p. 38, lines 27-32 of the present specification. Applicants argue that the in vivo data provide support that the claimed method will function as a therapeutic cancer drug.

Applicants' arguments have been considered, but have not been found persuasive. Although tumor growth and invasion are suppressed by a dominant negative UFO/AXL protein engineered to be expressed in a tumor cell *in vitro*, no evidence has been presented that such a mutant protein can be delivered to or expressed in a cancer cell *in vivo* without the prior engineering of the cells *in vitro*. Additionally no empirical evidence has been presented that an antibody or any other agents directed against AXL can reduce the invasivity of cancer cells *in vivo*. Thus, although one could predictably reduce the invasivity of cancer cells *in vitro* by inhibiting the AXL protein, given the unpredictability in the art of the development of cancer therapeutics and the refractory nature of cancer to drugs previously set forth, one of skill in the art one of skill in the art would not predictably be able to reduce the invasivity of cancer cells that are susceptible to AXL suppression *in vivo*.

Applicants argue that *in vitro* tests were conducted on MatrigelTM-matrix (3D outgrowth), as described in the references 101, 112, and 12 3 cited in the present application, in order to show morphologies and to assay invasion activity and migration ability. These tests are described at p. 20, line 23 - p. 22, line 3; p. 25, line 19- p. 26, line 5 of the present application. See also p. 9, line 1-15 and Figure 1; p. 11, line 25- p. 13, line 4 and Figures 5-7. Reference 10, in particular, describes the benefits and accuracy of using a MatrigelTM for measuring invasiveness of tumor cells, showing that this model predicts in vivo behavior. These in vitro tests on MatrigelTM showed that the dominant negative mutant of the AXL gene (dnAXL) strongly suppressed invasiveness, migration and survival of cells and that a polyclonal antibody directed against the extracellular portion of the AXL protein strongly inhibited migration and invasion of tumor cells. See p. 26, lines 14-31. Applicants argue that the above testing, both in vivo and in an in vitro assay known in the art to reliably predict in vivo activity, show that the skilled person would have been able to practice the invention as claimed

Applicants' arguments have been considered, but have not been found persuasive because *in vitro* assays are not reliably predictive of *in vivo* activity as previously set forth. Thus, although one could predictably reduce the invasivity of cancer cells *in vitro* by inhibiting the AXL protein, given the unpredictability in the art of the development of cancer therapeutics and the refractory nature of cancer to drugs previously set forth, one of skill in the art one of skill in the art would not predictably be able to reduce the invasivity of cancer cells that are susceptible to AXL suppression *in vivo*.

Applicants argue that the specification also discloses data showing that inhibited AXL protein function resulted in reduced invasivity. For example, western blot analysis demonstrated that an antibody directed against the human AXL protein inhibits AXL-mediated signaling (see p. 13, lines 6-18 and Figure 8; p. 28, line 18- p. 29, line 7; p. 32, line 21 - p. 33, line 13). In addition, a truncated, dominant-negative mutant form of human UFO/AXL lacking the intracellular RTK-bearing domain abolished Gas6/UFO/AXL-mediated signaling. See p. 13, lines 6-18; p. 32, line 21 - p. 33, line 13.

Applicants' arguments have been considered, but have not been found persuasive. The specification does not show that the AXL antibody inhibited AXL signaling, the AXL antibody was simply used for detection of the AXL protein in assays of the dnAXL's effect on signaling. Although a truncated, dominant-negative mutant form of human UFO/AXL lacking the intracellular RTK-bearing domain abolished Gas6/UFO/AXL-mediated signaling, no evidence has been presented that such a mutant protein can be delivered to or expressed in a cancer cell *in vivo* without the prior engineering of the cells *in vitro*. Additionally no empirical evidence has been presented that an antibody or any other agents directed against AXL can reduce the invasivity of cancer cells *in vivo*. Thus, although one could predictably reduce the invasivity of cancer cells *in vitro* by inhibiting the AXL protein, given the unpredictability in the art of the development of cancer therapeutics and the refractory nature of cancer to drugs previously set forth, one of skill in the art one of skill in the art would not predictably be able to reduce the invasivity of cancer cells that are susceptible to AXL suppression *in vivo*.

Applicants argue in the remarks of 10/14/2008 that the Examiner alleges that one of skill in the art would not predictably be able to reduce the invasivity of cancer cells that are susceptible to AXL suppression in vivo. Applicants disagree with the Examiner's allegation and submit herewith references, Voskoglou-Nomikos et al. (Clinical Research, vol. 9, 4227-4239, 2003) and Khleif et al. (Animal Models in Developmental Therapeutics, Chapter 42, p. 573-584, 2000), in support of the enablement of those skilled in the art to use the presently claimed methods at the time the invention.

Applicants argue that Voskoglou-Nomikos et al. assess the clinical predictive value of the in vitro cell line, human xenograft, and mouse allograft pre-clinical models. The results suggest that the in vitro cell line model is of at least equivalent usefulness to the human xenograft model (see page 4237, left column, second paragraph). Applicants argue that further, the authors argue

for "emphasis to be placed on in vitro cell lines (in the context of the NCI Human Tumor Cell Line Screen) and appropriate panels of the human xenograft model."

Applicants' arguments have been considered, but have not been found persuasive. The data on cell lines described by Voskoglou-Nomikos et al. using the NCI Human Tumor Cell Line Screen does not provide enabling support for the claimed method because the NCI Human Tumor Cell Line Screen is not drawn to examining tumor cell invasivity and examines a much larger sample of cells than presented in the instant specification. In particular, the NCI Human Tumor Cell Line Screen is a panel of 60 cell lines where each tumor is represented by a panel of cell lines and it is used to measure cell growth inhibition by the test compound, see p. 4228-1st col. and paragraph bridging p. 4229 and 4230. Furthermore, Voskoglou-Nomikos et al. teach that although the cell lines might be predictive of typical cytotoxic cancer drugs, it might fail to be predictive of non-cytotoxic drugs and that more study is needed, see paragraph bridging p. 4235-4236. Thus, given that Voskoglou-Nomikos et al. do not teach that studies of cell lines are predictive for methods of reducing invasivity of cancer cells and indicates that panels of cell lines are required to provides predictive information and that the data may not be applicable to non-cytotoxic drugs, which are being used in the instant method, the teachings of Voskoglou-Nomikos et al. do not provide enabling support for the invention as claimed.

Applicants argue that Khleif et al. discuss the role of animal models in drug discovery and drug screening. The reference describes that National Cancer Institute's (NCI) current cancer screening method as "an in vitro (Stage I) screen followed by the more refined in vivo (Stage II) screen" (see paragraph bridging pages 573-574). In particular, it can be seen from this reference

that the implantation of tumor cells is a generally accepted model for drug development. Further, the authors describe several approaches for tumor implantation (pages 577-578). On page 576, right column, 3rd full paragraph, Khleif et al. refer to the success of human tumor xenografting into nude mice as "revolutionizing many aspects of cancer research, including drug development." The reference further states "in fact, excellent correlations can be made between average growth delay for human tumors in nude mice treated with the best available drug combinations and complete clinical response rates"; studies using lung cancer, colon cancer, breast cancer, and malignant melanoma are cited (see page 577, 1st full paragraph). Moreover, Khleif et al. discuss the refinement of animal models in drug development over time, mentioning the "general convertibility of doses between species" (see page 581, right column, last paragraph).

Applicants' arguments have been considered, but have not been found persuasive because although animal models are generally accepted in drug development, as previously set forth, no evidence has been presented that demonstrates that in an appropriate animal model system that an antibody or any other agents directed against AXL can reduce the invasivity of cancer cells *in vivo*. Thus, Applicants' arguments have not been found persuasive and the rejection is maintained for the reasons previously set forth.

New Grounds of Rejection

Priority

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

7. The disclosure is objected to because of the following informalities: There are hyperlinks in the specification at p.17, line 22. Removal of the "http://" will disable the hyperlink and obviate this objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites the limitation "the inhibitor" in claim 10. There is insufficient antecedent basis for this limitation in the claim because claim 10 is drawn to "an inhibitor of the AXL gene, AXL ligand gene AXL protein and/or AXL protein ligand" and thus it is not clear to which of these inhibitors claim 19 is referring. Amendment of claim 19 to identify what an antibody directed against the AXL protein is inhibiting would obviate the instant rejection.

9. Claims 10, 12, 14, 17, 18 and 35 are rejected as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of reducing invasivity of cancer cells . . . comprising administering an inhibitor of the AXL protein. The claims lack any limitation on

said inhibitor of the AXL protein and thus are drawn to a genus of inhibitors of the AXL protein. When given the broadest reasonable interpretation, the term "inhibitor of the AXL protein" encompasses any "inhibitor of the AXL protein" such as a protein, peptide, antibody, low molecular weight, thus the genus of compounds is highly variant which vary significantly both in structure and function from each other. The description of a polyclonal antibody directed to the extracellular portion of AXL that inhibits the migration of cell lines *in vitro* (see p. 26-lines 24-28 and Fig. 6) fails to adequately describe the genus of agents because said genus tolerates members which differ significantly in both structure and function from said antibody to AXL protein One of skill in the art can reasonably conclude that applicant was not in possession of a genus of term "inhibitor of the AXL protein at the time the invention was filed. Because the genus of term "inhibitor of the AXL protein" is not adequately described, the method claims relaying on said genus are also not adequately described.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus

because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

It is noted that as of the filing date antibodies that inhibit AXL protein activity were known in the art (see U.S. Pat. No. 5,468,634 col. 7, line 60 to col. 8 line 30, previously cited), however, these antibodies fail to adequately describe an entire genus because the genus is highly variant encompassing members which differ significantly in structure from the few art known antibody inhibitors.

In the instant case the genus is only described as a definition by function (i.e. inhibition of AXL protein), and beyond the examples of antibodies, one of skill in the art cannot readily visualize or recognize the identity of members of the genus.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642